Guidelines for Immunosuppression Tapering in patients undergoing allogenic stem cell transplant for Hematological Diseases

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Institutional Guidelines for Immunosuppression Tapering in patients undergoing allogenic stem cell transplant for Hematological Diseases

1. Introduction:

In patients undergoing HSCT for malignancies, post-transplant immunosuppression (IS) is continued for a finite period of time to prevent graft versus host disease (GVHD). However, continued immunosuppression is marred with risk of delayed immune reconstitution which increases risk of infections as well as disease relapse. Timing of tapering IST is also critical to allow for graft versus leukemia effect (GVL) to set in. This is especially desirable in patients at high risk of relapse.

There is marked heterogeneity in IST discontinuation practice with variation in initiation of tapering, sequence of agents tapered, frequency of changes and strategy utilized. Other areas of controversial discussion in allogeneic stem cell transplantation are the target serum concentration of calcineurin inhibitor and schedule of calcineurin inhibitor and MMF tapering.

In this guideline we discuss the IS regimen and timing and duration of IS discontinuation with an aim to prevent relapse and avoid GVHD at the same time.

2. Prophylactic Regimen (3):

a. Prophylactic regimen for Allo BMT with MAC will consist of CSA with MTX / ATG. Day+11 MTX can be considered in patients without prohibitive mucositis.
b. Prophylactic regimen for Allo BMT with RIC will consist of CSA with MMF
c. Prophylactic regimen for Haploidentical BMT will consist of CSA with MMF and PTCy
d. CSA/ATG for AA/PNH

3. Target Serum Concentration of CSA

a. Careful monitoring with a standard laboratory assay and target serum conc of 200-300ug/l in the first four weeks post transplant to prevent acute GVHD. Subsequent serum concentration should be balanced between GVHD and relapse risk.
b. In standard GVHD risk HLA matched RIC Allo-BMT for hematological malignancies the recommended target CSA concentration after 4 weeks is 100-200 ug/l (twice daily dose). Higher target doses are needed with continuous infusion schedule.
c. Target CSA conc of 150-250ug/l for MAC Allo-BMT for hematological malignancies
d. Target CSA conc of 200-300 for AA/PNH till start of tapering.
e. **Sampling for CSA**
    i. Frequency of CSA Sampling will be twice weekly for 1st 4 weeks post transplant and then once weekly till CSA is tapered off
    ii. Sampling must be done as per SOP to avoid erroneous results
    iii. The sample must be done just before the next due dose to measure accurate nadir levels

4. IST Tapering:

a. CNI tapering will be decided on
   i. Risk of relapse of individual patient
   ii. T Cell chimerism
   iii. Risk factors for GVHD (see below)
   iv. Presence or absence of GVHD at the time of taper
b. In standard risk recipients of Allo-BMT for hematological malignancies improved outcomes were observed in patients who completed CSA tapering by 6 months (starting around day 90 if no GVHD)
c. Early CSA tapering starting between day 45 to 60 for patients at high risk of relapse
d. CSA is not tapered if signs of acute or chronic GVHD are present with the exception of mild cutaneous GVHD
e. Calcineurin inhibitor tapering for bone marrow failure, PNH and hemoglobinopathies should be started between 9 to 12 months post transplant and completed over next 3 months
f. Duration of MMF prophylaxis is about 30 days in MRD and 2-3 months in MUD (based upon relapse and GVHD risk).

5. Duration of post-HSCT IST:

a. The duration of post-transplant IST for hematological malignancies should be within 6 months in total for non-high risk patients.
b. The duration of post-transplant IST for hematological malignancies should be 3 months in total for high risk patients.
c. Duration of IST for non malignant disorders should be around one year

6. Defining High Risk patients

Any patient with high risk of relapse or any patient with mixed T-cell chimerism at day 30 or 60 post HSCT

a. **Risk of relapse:** The risk of relapse will be decided on the following
   i. High risk cytogenetics at diagnosis as per ELN Criteria (1)
   ii. Response to chemotherapy (ref: Front. Oncol., 15 April 2021 | https://doi.org/10.3389/fonc.2021.666091)
   iii. MRD Status Pre and post-transplant
   iv. Conditioning regimen (MAC vs RIC)

b. Chimerism:

   i. Lineage specific will be measured at day 30, 60 and 100
   ii. T cell chimerism less than 95% will lead to early IST tapering followed by reassessment of chimerism after 4 weeks for hematological malignancies and increasing IS for AA

iii.

iv. Increasing mixed chimerism despite IS tapering can also lead to consideration of DLI as per protocol

c. **GVHD Risk factors (2):**

Presence of any of these factors should lead to consideration against early tapering

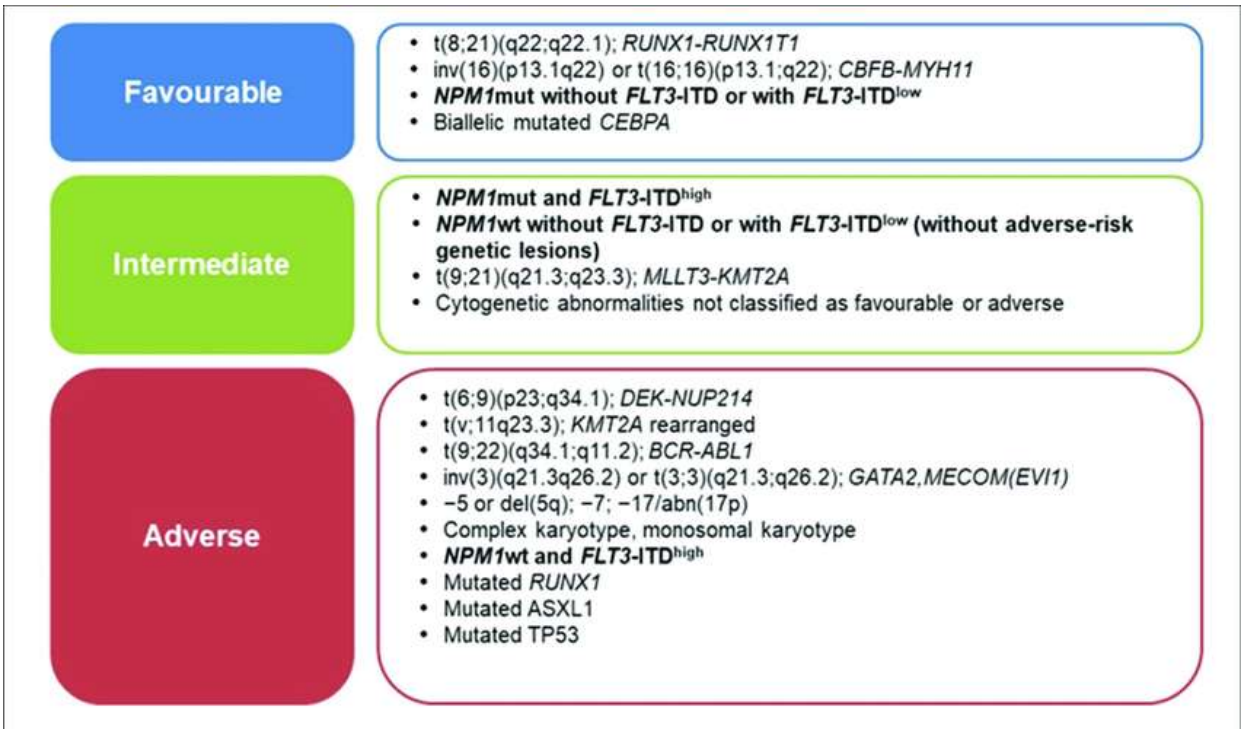
i. Age of patient or more
ii. Age of donor 40 or more
iii. Multiparous donor
iv. Myeloablative conditioning
v. Use of PBSC
vi. Clinical evidence of GVHD:

Clinical evidence of GHVD at the time of tapering will lead to delay in taper except for mild skin GVHD

7. Interventions for impending graft failure and disease relapse:

a. Aplastic anemia and Hemoglobinopathies
   i. For patients with increasing mixed chimerism and drop in hemoglobin, Optimize/ increase immunosuppression
   ii. For patients with low counts and full donor chimerism, consider stem cell boost till day 100.
   iii. There is limited evidence to support use of DLI in benign disorders
b. Malignancies
   i. for patients with increasing mixed donor chimerism, it is recommended to rapidly taper IST /withdraw IST
   ii. If complete chimerism is not achieved 4-8 weeks post IST cessation, consider DLI
   iii. Consider early DLI in patients with high risk of disease relapse (transplanted in MDS-EB2, MRD +ve disease)

Figure 1



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